REMARKS/ARGUMENTS

I. Status of the claims

With entry of this Amendment, claims 25 and 31 are amended, claim 32 is canceled and claims 42-49 are introduced. Claims 25-31 and 33-49 are currently pending. Claims 34-41 have been withdrawn by the Examiner. Claims 25-31, 33 and 42-49 are being examined.

II. Support for the amendments

Amendments to the claims made in this amendment find support in canceled claim 32 and throughout the specification and previously-pending claims. Claim 42 finds additional support in paragraphs 27 and 128, and Example 6 of the specification. The amendments introduce no new matter into the specification.

III. Interview

Applicants thank the Examiner for the phone interview on October 30, 2007. Applicant's counsel and the Examiner discussed the "walking" method (described below) with respect to the pending claims.

IV. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 25-33 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description and enablement requirements.

A. The Claimed Invention

Claims 25 and 42 are the only independent claims currently under examination by the Examiner. All other claims under examination are dependent on claim 25 or 42, or another dependent claim. Claims 25 and 42 are identical except claim 25 is limited to LDL-receptor class A monomer domains and claim 42 is limited to C2 monomer domains. Claims 25 and 42 are reproduced below.

25. A method for identifying a multimer that binds to a target molecule, the method comprising,

providing a library of polypeptides, the polypeptides comprising LDL-receptor class A monomer domains, wherein the monomer domains consist of 30-100 amino acids;

screening the library of polypeptides for affinity to a target molecule;

identifying at least one polypeptide comprising a first LDL-receptor class A monomer domain that specifically binds to a target molecule;

linking the first LDL-receptor class A monomer domain to a plurality of additional LDL-receptor class A monomer domains to form a library of LDL-receptor class A multimers, the multimers comprising the first monomer domain and one of the plurality of additional monomer domains;

screening the library of multimers for the ability to bind to the target molecule; and

identifying a multimer that specifically binds to the target molecule.

42. A method for identifying a multimer that binds to a target molecule, the method comprising,

providing a library of polypeptides, the polypeptides comprising C2 monomer domains, wherein the monomer domains consist of 30-100 amino acids;

screening the library of polypeptides for affinity to a target molecule;

identifying at least one polypeptide comprising a first C2 monomer domain that specifically binds to a target molecule;

linking the first C2 monomer domain to a plurality of additional C2 monomer domains to form a library of C2 multimers, the multimers comprising the first monomer domain and one of the plurality of additional monomer domains;

screening the library of multimers for the ability to bind to the target molecule; and

identifying a multimer that specifically binds to the target molecule.

B. *Analysis – Written Description*

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. Possession may be shown in a variety of ways including description of an actual reduction to practice. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998).

In the present case, the Applicants have shown actual reduction to practice of the claimed invention. Claims 25 and 42 encompass a method referred to as to as "walking" (see steps in claims 25 and 42 starting with "linking..."), described, *e.g.*, at paragraph 230 on page 65 of the specification:

> [230] When multimers capable of binding relatively large targets are desired, they can be generated by a "walking" selection method. This method is carried out by providing a library of monomer domains and screening the library of monomer domains for affinity to a first target molecule. Once at least one monomer that binds to the target is identified, that monomer is covalently linked to a new library or each remaining member of the original library of monomer domains. This new library of multimers (dimers) is then screened for multimers that bind to the target with an increased affinity, and a multimer that binds to the target with an increased affinity can be identified. The "walking" monomer selection method provides a way to assemble a multimer that is composed of monomers that can act additively or even synergistically with each other given the restraints of linker length. This walking technique is very useful when selecting for and assembling multimers that are able to bind large target proteins with high affinity. The walking method can be repeated to add more monomers thereby resulting in a multimer comprising 2, 3, 4, 5, 6, 7, 8 or more monomers linked together.

Applicants have actually reduced the claimed method to practice. For instance, Example 11 (pages 107 to 111 of the specification) describes the development of CD28-specific LDL receptor-based A domains and dimers by "walking." The steps followed in this Example follow the steps of the method claimed in the present invention. The applicants provided a library of DNA sequences encoding monomeric A domains. The applicants screened the library of polypeptides for affinity to a target molecule by coating individual wells of a 96-well microtiter plate with target protein (e.g., CD28) and after blocking, adding purified phage and incubating followed by washing. Bound phages were eluted and the phage eluate was amplified to identify at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule. The monomer fragments were then 'walked' to dimers by attaching a library of naive A domain fragments using DNA ligation, thereby forming a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of

different monomer domains. The multimer library was then screened as described above, and binding of the individual phage clones to their target proteins was analyzed by ELISA. Multimers were thus identified which specifically bound to the target molecule, where the multimer comprises the first monomer domain and a second monomer domain. As further described in Example 11; a subset of these clones was then used in efficacy assays using human and monkey PBMC, and demonstrated inhibition activity in those assays.

In an effort to expedite prosecution, the pending claims have been amended to introduce limitations to LDL-receptor class A monomer domains (in the case of claim 25 and its dependent claims) or C2 monomer domains (in the case of claim 42 and its dependent claims), where the monomer domains in each set of claims consist of 30-100 amino acids.

In view of the foregoing, the Applicants maintain that the pending claims comply with the written description requirement, and respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph

C. *Analysis – Enablement*

To satisfy the enablement requirement, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'. In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

In the present case, the Examiner has stated that the specification is enabling for generating libraries of monomers and/or multimers based on LDL receptor A domains alone, and C2 domains alone (Office action mailed August 9, 2007, page 9, first paragraph). In an effort to expedite prosecution, the pending claims have been amended to introduce limitations to LDL-receptor class A monomer domains (in the case of claim 25 and its dependent claims) or C2 monomer domains (in the case of claim 42 and its dependent claims).

In view of the foregoing, the Applicants respectfully submit that the pending claims under examination comply with both the written description and enablement requirements, and respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

V. Rejections under 35 U.S.C. § 102

The Examiner rejected claims 25, 27, 28, 30, 31, and 33 under 35 U.S.C. §102(b) as anticipated by Barbas, *et al.* (US 6,140,466; 10/31/2000). The Examiner further rejected claims 25-30, 32, and 33 under 35 U.S.C. §102(b) as anticipated by Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988). The Examiner further rejected claims 25-33 under 35 U.S.C. §102(b) as anticipated by Bajari, *et al.* (Biological Chemistry. Vol. 379: 10153-10162; 1998). The Examiner further rejected claims 25-31 and 33 under 35 U.S.C. §102(e) as anticipated by Etzerodt, *et al.* (US 2004/0132094 A1; 7/8/2004; alleged priority date: 2/28/2001).

A. The Present Invention

See "*The Claimed Invention*" under Section IV(A), above.

B. Barbas, et al.

Barbas, *et al.*, teach a polypeptide linker that fuses two three-finger Zinc finger proteins – two six-fingered proteins were created and demonstrated to bind 18 contiguous bp of DNA in a sequence specific fashion. Barbas, *et al.*, further teach that expression of these proteins as fusions to activation or repression domains allows transcription to be specifically up or down modulated within cells, and that polydactyl zinc finger proteins are broadly applicable as genome-specific transcriptional switches in gene therapy strategies and the development of novel transgenic plants and animals. Barbas, *et al.*, additionally disclose that such proteins are useful for inhibiting, activating or enhancing gene expression from a zinc finger-nucleotide binding motif containing promoter or other transcriptional control element, as well as a structural gene or RNA sequence. Barbas, *et al.*, also teach a method for obtaining an isolated zinc finger-

nucleotide binding polypeptide variant which binds to a cellular nucleotide sequence, comprising identifying the amino acids in a zinc finger-nucleotide binding polypeptide that bind to a first cellular nucleotide sequence and modulate the function of the nucleotide sequence; creating an expression library encoding the polypeptide variant containing randomized substitution of the amino acids identified; expressing the library in a suitable host cell; and isolating a clone that produces a polypeptide variant that binds to a second cellular nucleotide sequence and modulates the function of the second nucleotide sequence.

Barbas, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule. Furthermore, Barbas, *et al.*, teach nothing about C2 or LDL-receptor class A monomer domains.

C. Esser, *et al.*

Esser, *et al.*, teach a mutational analysis of the ligand binding domain of the low density lipoprotein (LDL) receptor. According to Esser, *et al.*, the ligand binding domain of the LDL receptor contains seven imperfect repeats of a 40-amino acid cysteine-rich sequence (referred to by Esser, *et al.*, as Repeats 1-7). To dissect the contribution of these different cysteine-rich repeats to ligand binding, Esser, *et al.*, used oligonucleotide-directed mutagenesis to generate nine substitution mutations (each as a separate construct) in the ligand binding domain.

Esser, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening

the library of multimers for the ability to bind to the target molecule.

D. *Bajari, et al.*

Bajari, *et al.*, define the minimal binding domain of the multifunctional chicken oocyte receptor for yolk deposition (termed LR8), a relative of the low density lipoprotein receptor (LDLR). Bajari, *et al.*, used phage display of fragments derived from the entire LR8 receptor molecule and panning on the ligand -- receptor associated protein (RAP) -- to define an 80 residue stretch LR8 minireceptor. The 80 residue stretch contains 12 cysteines, and represents parts of the second, the entire third, and parts of the fourth, of the eight clustered 'ligand binding repeats' in LR8. Bajari, *et al.*, state that in addition to its use in defining minimal binding domains, the phage display approach provides powerful tools for dissection, and consequently, manipulation, of the function of receptors so as to direct their binding activity toward ligands of diagnostic and/or therapeutic interest. The reference also teaches that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far.

Bajari, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule.

E. *Etzerodt, et al.*

Etzerodt, *et al.*, teach a family of protein libraries comprising CTLDs (C-type Lectin-Like Domains), e.g., Tetranectin CTLDs, in which internal polypeptide loop-regions lining the ligand binding sites in CTLDs have been replaced with ensembles of completely or partially randomized polypeptide segments. Etzerodt, *et al.*, further teach the generation and

manipulation of human and murine tetranectin CTLD libraries, as well as phagemid vectors useful in the generation and manipulation of human and murine tetranectin CTLD libraries. The reference also teaches that CTLD derivatives with affinity for new ligands may readily be isolated from libraries of vectors displaying CTLDs, in which loop-regions have been randomized, using one or more rounds of enrichment by screening or selection followed by amplification of the enriched subpopulation in each round.

Etzerodt, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule. Furthermore, Etzerodt, *et al.*, teach nothing about C2 or LDL-receptor class A monomer domains.

F. Analysis

For anticipation under 35 U.S.C. §102, a single reference must teach every aspect of the claimed invention. The methods encompassed by the claimed invention are directed to the making and screening of a "walked" multimer library, where the multimer library was generated using monomer domain(s) that bound to a first target molecule and linking such a first monomer domain to a plurality of different monomer domains to form a library of different multimers. None of Barbas, *et al.*, Esser, *et al.*, Bajari, *et al.*, or Etzerodt, *et al.*, teach such "walked" libraries or methods of using them to identify a multimer (or any molecule) that binds to a target molecule. Furthermore, the claimed methods are limited to C2 monomer domains and LDL-receptor class A monomer domains. Neither Barbas, *et al.*, nor Etzerodt, *et al.*, mention anything about C2 monomer domains or LDL-receptor class A monomer domains. Since none of these references teach these elements of the claimed methods, the Applicants respectfully submit that none of Barbas, *et al.*, Esser, *et al.*, Bajari, *et al.*, or Etzerodt, *et al.*, anticipate the pending claims. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

VI. Rejections under 35 U.S.C. § 103

The Examiner rejected claims 25-33 under 35 U.S.C. §103(a) as unpatentable over Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari, *et al.*, (Biological Chemistry. Vol. 379: 10153-10162; 1998).

A. *The Present Invention*

See above.

B. *Esser, et al.*

See above.

C. *Bajari, et al.*

See above.

D. *Analysis*

As noted above, the primary reference of Esser, *et al.*, does not teach any "walked" libraries or any methods of using such walked libraries. This failing is not remedied by the secondary references of Bajari, *et al.*

The Examiner asserts that "the features upon which applicant relies (i.e., "walked multimer library") are not recited in the rejected claim(s)." Applicants respectfully submit that this is incorrect. The claimed invention (independent claims 25 and 42) includes the step of *linking the first (C2 or LDLR) monomer domain to a plurality of additional (C2 or LDLR) monomer domains to form a library of (C2 or LDLR) multimers, the multimers comprising the first monomer domain and one of the plurality of additional monomer domains*. This step is the essence of the walked library approach described in the specification and summarized above: after identifying at least one monomer that binds to a target, that monomer is covalently linked to a new library or each remaining member of the original library of monomer domains. This new library of multimers (dimers) is then screened for multimers that bind to the target with an increased affinity, and a multimer that binds to the target with an increased affinity can be identified. Neither Esser, *et al.*, nor Bajari, *et al.* teach or suggest this approach to making libraries.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection(s) under 35 U.S.C. §103.

VII. Double Patenting

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15-17, and 20-26 of copending Application No. 11/281,256 (200602342 99; filed 11/16/05).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 11/281,245 (20060223114; filed 11/06/05).

The Examiner provisionally rejected claim 25 and 33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 207-214 of copending Application No. 10/966,064 (20050221384; filed 10/15/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-32 of copending Application No. 10/971,679 (20050164301; filed 10/22/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 21, 29, 33, 36, 78, and 98 of copending Application No. 10/871,602 (20050089932; filed 6/17/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 13, 16, 23, 29, 33, 36, 78, and 98 of copending Application No. 10/840,723 (20050053973; filed 5/5/2004).

The Examiner provisionally rejected claim 25, 26, and 28-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18, 21-24, 29-31 and 34-36 of copending Application No. 10/957,351 (20060008844; filed 1/12/2006).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 18-21, and 24-27 of copending Application No. 11/155,989 (20060177831; filed 6/17/05).

The present application was filed on 10/24/2003. Where a provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application may be rejectable on other grounds, the MPEP (§804) instructs the Examiner to withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. Accordingly, the Applicants respectfully request the Examiner to withdraw this provisional nonstatutory obviousness-type double patenting rejection and allow this application to issue.

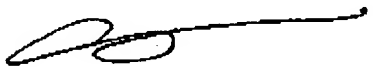
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 650-244-3147.

The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,



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